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(54) Sustained releas therapeutic compositions based on high molecular weight hydroxypropylmethylcellulose

(57) The invention relates to a carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon administration. The carrier base material is one or more hydroxypropylmethylcelluloses or a mixture of one or more hydroxypropylmethylcelluloses and up to 30% by weight of the mixture of methylcellulose, sodium carboxymethylcellulose and/or other cellulose ether. At least one of the hydroxypropylmethylcelluloses has a methoxy content of 16—24 weight-%, a hydroxypropoxyl content of 4—32 weight-% and a number average molecular weight of at least 50,000. The carrier base material constitutes less than about one third of the weight of the solid unit dosage form.

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SPECIFICATION

Sustained release therapeutic compositions based on high molecular weight hydroxypr pylmethylcellul se

This invention relates to a carrier base material to be combined with a therapeutically active medicament and formed into a solid, shaped dosage unit having a long-lasting and regular incremental release of the medicament upon administration. Specifically, this invention relates to a carrier base material, consisting essentially or predominantly of hydroxypropylmethylcellulose having a chemical structure and molecular weight which render it suitable for use, in relatively low concentrations, in sustained release therapeutic compositions.

Hydroxypropylmethylcelluloses are commercially available in various grades, under several tradenames, including Methocel E, F, J and K (all previously designated as Methocel HG) from The Dow Chemical Co., U.S.A., HPM from British Celanese Ltd., England, and Metalose SH from Shin-Etsu, Ltd., Japan. The various grades available under a given tradename represent differences in methoxyl and hydroxypropoxyl content as well as molecular weight. The methoxyl content ranges from 16.5 to 30 weight-% and hydroxypropoxyl content ranges from 4 to 32 weight-%, as determined by the method described in ASTM D-2363-72.

Commercial designations of the various hydroxypropylmethylcelluloses are based on the viscosities of 2% aqueous solutions at 20°C. The viscosities range from 15 cps to 30,000 cps and represent number average molecular weights ranging from about 10,000 to over 150,000, as calculated from the data in "Handbook of Methocel Cellulose Ether Products" (The Dow Chemical Co., 1974).

A solid unit dosage form consisting of a mixture of a medicament and a carrier base material which is low molecular weight hydroxypropylmethylcellulose Methocel E50, formerly known as Methocel 60HG 50 cps, having a number average molecular weight of 23,000, a methoxyl content of 28—30 weight-% and a hydroxypropoxyl content of less than 9 weight-%, rapidly releases the medicament when brought into contact with the aqueous fluids of the mouth of the gastrointestinal tract. However, an effective "sustained release" tablet is produced by admixture of a medicament with a modified Methocel E50, per se or in admixture with other cellulose ethers. As disclosed by Lowey and Stafford (U.S. Patent 3,870,790) and Schor (U.S. patent 4,226,849), the modification is carried out by exposure of the low molecular weight hydroxypropylmethylcellulose Methocel E50 to high humidity or moisture and drying in air.

In our co-pending U.K. Patent Application No. 82,35858 it was disclosed that effective prolonged release therapeutic compositions may be prepared by using as a carrier base material a hydroxypropylmethylcellulose having a hydroxypropoxyl content of 9—12 weight-% and a number average molecular weight of less than 50,000, e.g. Metalose 60SH50. The carrier base material provides sustained release characteristics without treatment or modification.

Christenson and Huber (U.S. Patent No. 3,590,117) reported that high visocity grade, i.e. 15,000 cps, hydroxypropylmethylcellulose did not make an acceptable long-lasting troche because the troche would flake off in the mouth rather than dissolve uniformly.

Christenson and Dale (U.S. Patent No. 3,065,143) disclosed the use of certain high molecular weight hydrophilic gums, including hydroxypropylmethylcelluloses, in the preparation of a "sustained release tablet". The tablet consisted essentially of a mixture of a medicament and at least one third part by weight of the weight of the tablet of a hydrophilic gum which rapidly absorbed water and swelled at 37°C to form a "soft mucilaginous gel barrier" on the surface of the tablet when brought into contact with the aqueous fluids of the gastrointestinal tract.

The high molecular weight hydroxypropylmethylcelluloses disclosed by Christenson and Dale and consisting at least one third of the weight of the tablet include Methocel 60HG 4000 cps, now known as Methocel E4M, having a 28—30 weight-% methoxyl content, a 7.5—12 weight-% hydroxypropoxyl content and a number average molecular weight of 93,000, and Methocel 90HG 4000 cps and Methocel 90HG 15,000 cps, now known as Methocel K4M and Methocel K15M, respectively. The latter have number average molecular weights of 89,000 and 124,000 respectively, and a 19—24 weight-% methoxyl content, and a 4—12 weight-% hydroxypropoxyl content.

The present invention is directed toward further improvement in carrier base materials containing hydroxypropylmethylcelluloses for use in the preparation of sustained release solid pharmaceutical unit dosage forms, particularly with moisture-sensitive and/or high dosage medicaments.

An object of the present invention is to provide a carrier material for use in the preparation of orally, bucally or sublingually, etc., administered lozenges and tablets, as well as suppositories and other solid dosage forms which have a regular and sustained release pattern for a systematically absorbable medicament or active ingredient incorporated therein.

Another object of the present invention is to provide a carrier base having greater stability, greater hardness, lower friability, reduced water solubility and a uniform sustained release pattern from hydroxypropylmethylcellulose, particularly for use with moisture-sensitive medicaments.

A further object of the present invention is to provide a carrier base which comprises less than about 30 weight-% of the weight of the solid unit dosage form, permitting the preparation of smaller

units which are easier to administer.

Still another object of the present invention is to provide a carrier base for use with high dosage medicaments in sustained release dosage forms.

We have now found that these improvements in a carrier base can be achieved by utilizing a high viscosity grade hydroxypropylmethylcellulose having a number average molecular weight above 50,000 and a methyl content of 16—24 weight-%, wherein said carrier base constitutes less than about one third of the weight of the sustained release dosage form.

According to the present invention, it has now been found that important advantages and improvements over prior products containing hydroxylpropylmethylcelluloses, as described in U.S. Patents Nos. 3,065,143, 3,870,790 and 4,226,849, can be obtained by utilizing a high viscosity grade hydroxypropylmethylcellulose having a methoxyl content of 16—24 weight-%. The hydroxypropylmethylcellulose used in the present invention has a number average molecular weight above 50,000 and a hydroxypropoxyl content of 4—32 weight-%.

The hydroxypropylmethylcelluloses which are effective in the present invention include, but are not limited to, commercially available 4000 and 15,000 cps viscosity grades of Methocel K, i.e. Methocel K4M and Methocel K15M, available from the Dow Chemical Co., U.S.A., and 4000, 15,000 and 30,000 cps viscosity grades of Metalose 90SH, available from Shin-Etsu Ltd., Japan, as well as 5,000, 12,000, 20,000 and 75,000 cps viscosity grades of Methocel J, i.e. Methocel J5M, J12M, J20M and J75M, available from the Dow Chemical Co.

Although U.S. Patent No. 3,065,143 disclosed that a sustained release tablet required the presence of at least one third of the weight of the table of these hydroxypropylmethylcelluloses, we have surprisingly found that effective sustained release can be obtained from solid dosage forms containing as little as 5 to about 30 weight-% of these hydroxypropylmethylcelluloses.

Numerous advantages result from the ability to use less than about 30% of the carrier base material in a sustained release dosage form. These include the use of smaller tablets which are more economical and are easy to administer. High dosage drugs which normally result in large tablets can be put in smaller sustained-release dosage form.

Cellulose ethers such as hydroxypropylmethylcelluloses of the present invention are hydrophilic and tend to absorb moisture from the atmosphere. The use of low levels of the cellulose ether in a solid dosage form results in a lower moisture content upon exposure to the atmosphere. This is particularly important when the active medicament is moisture-sensitive and undergoes decomposition and/or hydrolysis upon contact with moisture. Typical moisture-sensitive drugs include aspirin, phenacetin, procainamide, nikethamide, polymixin, barbiturates, idoxuridine, hydantoins, angiotensinamide, nitroglycerin, benzocaine, scopolamine, meperidine, codeine, streptomycin, ascorbic acid, sulphonamide drugs, tolbutamide, antihistamine salts such as chlorpheniramine and brompheniramine, phenylephrine, diphenhydramine, diethylcarbamazine, theophylline, caffeine, alkaloid salts, adrenocortical steroid esters such as hydrocortisone phosphate, and the like.

The hydroxypropylmethylcelluloses of the present invention may be used without prior humidification or similar treatment and, when mixed with an active medicament, the mixture has excellent compressibility and the tablets prepared therefrom are hard and dense, have low friability and provide sustained release over an extended period. Treatment of the carrier base material by humidification and drying before incorporation in a sustained release tablet has little or no effect on the compressibility of the polymer and the properties of the tablets prepared therefrom.

Sustained release drug forms containing the hydroxypropylmethylcelluloses of the present invention are stable and the release rate does not change over an extended storage period. The therapeutic compositions of the present invention, in most cases, give a steady, reproducible release of the active medicament.

A hydroxypropylmethylcellulose having a methoxyl content of 16—24 weight-% and a number average molecular weight above 50,000 can be used as the sole carrier base material or can be used in admixture in all proportions with other hydroxypropylmethylceluloses of the same structure with a higher or a lower but above 50,000 number average molecular weight, e.g. a 30/70 or 70/30 mixture of Methocel K4M and Methocel K15M. A hydroxypropylmethylcellulose having a different structure and a number average molecular weight above 50,000 can also be used in admixture with the high molecular weight hydroxypropylmethylcellulose having a methoxyl content of 16—24 weight-%, e.g. a 30/70 or 50/50 mixture of Methocel E4M and Methocel K4M.

The hydroxypropylmethylcelluloses of the present invention can be optionally mixed with about 0 to 30% by weight of the mixture of a hydroxypropylmethylcellulose with the same or different structure and a number average molecular weight below 50,000, or methylcellulose, sodium carboxymethylcellulos or other cellulose ether.

The active ingredient can be of any type of medication which acts locally in the mouth or systemically, and which, in the latter case, can be administered orally to transmit th active medicament into the gastrointestinal tract and into the blood, fluids and tissues of the body without excessive peak concentrations occurring. Alternatively, the active ingredient can be of any type of medication which acts through the buccal tissues of the mouth to transmit the active ingredient directly into the blood stream thus avoiding first pass liver metabolism and by-passing the gastric and intestinal fluids which

have an adverse inactivating or destructive action on many active ingredients unless they are specially protected against such fluids as by means of an enteric coating or the like. The active ingredient can also be of a type of medication which can be transmitted into the blood circulation through the rectal tissues.

Representative active medicaments include antacids, anti-inflammatory substances, coronary vasodilators, cerebral vasodilators, peripheral vasodilators, anti-infactives, psychoteoptics, anti-manics stimulants, antihistamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodilators, antiarrythmics, anti-hypertensive drugs, vascoconstrictors and migraine treatments, anti-coagulants and antithrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoletic drugs, antiasthmatics, expectorants, cough suppressants, mucolytics, antiuricemic drugs, and other drugs or substances acting locally in the mouth, such as topical analgetics, local anesthetics, etc.

The hydrpropylmethylcelluloses of the present invention are particularly effective in the preparation of sustained release unit dosage forms containing moisture-sensitive medicaments such as those named ealler. However, it is to be understood that the invention is applicable to sublingual lozenges, suppositories and compressed tablets, the latter intended to be swallowed in unit dosage and which upon ingestion according to a prescribed regimen give slow and regular release of active medicament while being protected against normally inactivating gastric fluids.

The hydroxypropylmethylcellulose having a methoxyl content of 16—24 weight-%, a number average molecular weight of more than 50,000 and which is present in a concentration of less than about one-third of the total weight of the dosage form, forms what is called a long-acting, slow dissolving carrier of such a nature that it has a protective, demulcent and buffering effect in the body and causes the active medicament to exert its optimum therapeutic action immediately and incrementally for many hours, so that full therapeutic advantage can be taken of the entire or substantially the entire amount of active medicament adminstered.

This unexpectedly high degree of efficiency is a particular advantage of the invention and minimizes the side effects of the medication.

In making up tablets containing an orally administerable systemically absorbable active component such as one of the heretofore mentioned medicaments, the oral carrier material is thoroughly intermixed with the medicament which is also in powdered or granular form or in solution, and any other necessary ingredients which are conventional in tablet making, such as magnesium stearate, lactose, starch and, in general, binders, fillers, disintegrating agents and the like. The complete mixture, in an amount sufficient to make a uniform batch of tablets, e.g. 50,000 each of which contains an effective amount of active medicament, is then subjected to tableting in conventional tableting machines at compression pressure of 2000 to 16000 lbs/sq. in. (138 to 1103 bar) and, because of the use of the specific carrier material of this invention in the production of the tablets, a product is obtained which has the desired hardness, low level of friability and a predetermined prolonged action and a regular delayed release pattern, so that the medicament is available over a period of 1 to 36 hours, depending on the precise tablet size, hardness and particular carrier composition. In this way, it is possible to produce sustained or slow continuous release tablets in relatively simple and economical manner on a commercial scale as contrasted with the more elaborate and more complex materials and procedures heretofore employed or proposed.

The moisture content of the carrier used in the preparation of the sustained release tablets may be in the 0.1—10% range, the lower end of the range being preferable when moisture-sensitive medicaments are used. If the moisture content is outside of this range, it may be brought within the range by the use of ambient or hot, dry or wet air, using appropriate equipment including static, convection, forced air or vacuum chambers or other equipment well known to those skilled in the art. The moisture content of the carrier during tableting influences the integrity of the tablet obtained under a given compression pressure. However, the moisture content has little or no influence on the sustained release characteristics and plays a minor role as compared to the chemical structure of the carrier and its concentration on the rate of release of medicaments. Similarly, while the release rate is governed at least in part by the size of the tablet or other shaped dosage form, as well as by the degree of compression, the chemical structure of the hydroxypropylmethylcellulose superimposes its effect and is the dominant factor in the control of the release rate.

The release pattern of active medicament from the carrier of the present invention can be controlled according to the particular medication and its intended therapeutic effect. For a sublingual lozenge or tablet, th release pattern may be varied from ab ut 15 minutes to about 4 hours. For orally administered tablets, the rate f release may be 2—4 hours, 4—8 hours, 8—10 h urs, 10—12 h urs, 15—18 hours, 20—24 hours, etc., as desired. For vaginal and rectal suppositories, the release pattern ranges from 2 to 36 hours, and can be less where indicated. Predetermined release patterns of unusually reliabl and constant characteristics can b secured. This is often very important medically, especially when treating patients having coronary diseases, such as angina pectoris with nitr glycerin, or related problems of circulatory disorders or abnormal blood pressure conditions or psychotropic

disorders such as manic depression or schizophrenia. The invention is particularly important also in treating such conditions as ulcerated tissues or mucous lesions and other conditions which arise from local hyperacidity or metabolic dysfunction in the physiological system. The invention is therefore of very versatile and adaptable nature giving it a wide range of application and end use.

The following illustrative embodiments of th disclosures of the present invention are non-limiting and variations will b obvious to thos skilled in the art.

Examples 1—6 describe the preparation of controlled release 650 mg aspirin tablets.

EXAMPLES 1—2

Controlled release 650 mg aspirin tablets containing 13.2% Methocel K4M were prepared from untreated Methocel K4M having a moisture content of 2.5% and from treated Methocel K4M which has been exposed to 85% humidity for 24 hours and then dried in a forced air oven at 120°F (49°C) to a moisture content of 5.0%.

The 650 mg aspirin tablets were prepared from the following ingredients:

	ingredients	grams	mg/tablet
1	Aspirin (40 mesh)	1300	650
2	Methocel K4M	200	100
3	Hydrogenated vegetable oil (Lubritab)	14	7
4	Fumed silica (Cab-O-Sil M-5)	1	0.5

Ingredients 1 and 2 were mixed, ingredient 3 was added to the blend and, after mixing, was followed by ingredient 4. The mixture was blended for 20 minutes and then subjected to compression in a tableting machine having a 0.281 × 0.625 inch (7.14 × 15.88 mm) punch, under a compression pressure of 4000 psi (276 bar), to make 2000 capsule shaped tablets bisected on one side. The average weight of the tablets was 760 mg from untreated Methocel K4M and 750 mg from treated Methocel K4M. The thickness of the tablets was 0.265—0.280 inches (6.73—7.11 mm) from the former and 0.260—0.265 inches (6.60—6.73 mm) from the latter.

The hardness of the tablets was determined on a Pennwalt Stokes hardness tester. The friability was determined in a Erweka Friabilator (Erweka-Apparatebau GmbH, Heuenstamm Kr. Offenbach/Main, West Germany) by measuring the weight loss after 3 minutes rotation.

The release rate was determined by using the release rate apparatus as described in NF XIV, page 985. Five tablets were placed into a 100 ml screw cap dissolution vial and 60 ml of a buffered solution of the desired pH, preheated to 37°C, was added to the vial. The vial was closed and rotated in the NF time release apparatus maintained at 40 ± 2 rpm. At intervals of one hour, the vial was opened and the supernatant liquid was poured through a screen and collected. The collected liquid was quantitatively transferred to a 100 ml volumetric flask. The tablets on the screen and the vial were washed with deionized water, the washings being added to the flask. The washed tablets were returned to the vial from the screen with the aid of the next buffered solution and the closed vial was rotated in the bath for the next interval of one hour. The following schedule of buffered solutions was used:

Hours	pH	Hours	pH
1	1.2	9	7.5
2	2.5	10	7.5
3	4.5	11	7.5
4	4.5	12	7.5
5	7.0	13	7.5
6	7.0	14	7.5
7	7.5	15	7.5
8	7.5	16	7.5

The solutions separated from the tablets were analyzed for the concentration of medicament released from the tablets. The procedure was continued until at least 90% of the tablet had dissolved and/or essentially all f the medicament had been released.

The 650 mg aspirin tablets had the following properties:

Example No.	1		1	
Methocel K4m	Untreated		Treated	
Hardness, kg	7.5—8.5		9.0—10.0	
Friability, %	0.4		0.26	
Release Rate Hour	%	Cumulative %	%	Cumulative %
1	8.9	8.9	10.8	10.8
2	11.6	20.5	10.8	21.6
3	10.6	31.1	12.0	33.6
4	10.2	41.3	10.7	44.3
5	12.4	53.7	13.5	57.8
6	8.3	62.0	10.7	68.5
7	13.6	75.6	9.4	77.9
8	7.5	83.1	5.5	83.4
9	3.8	86.9	4.3	87.7
10	3.0	89.9	3.3	91.0
13	—	—	—	98.1
14	—	100.9	—	—

Although the controlled release tablets prepared with treated and untreated Methocel K4M had comparable properties and release rates, the storage stability of the aspirin made with the treated carrier base material was about 18 months while that made with the untreated carrier base material was more than 3 years.

EXAMPLES 3—4

Controlled release 650 mg aspirin tablets containing 9.0% Methocel K4M were prepared from treated Methocel K4M which had been exposed to 85% humidity for 24 hours and then dried in a forced air oven at 120°F (49°C) to a moisture content of 5.0% and from treated Methocel K4M which was dried in an oven at 210°F (99°C) to a moisture content of 2.3%.

The 650 mg aspirin tablets were prepared from the following ingredients:

	Ingredients	Treated Methocel grams	Treated Dried Methocel grams	mg/tablet
1	Aspirin (40 mesh)	6500	650	650
2	Methocel K4M	650	65	65
3	Lubritab	70	7	7
4	Cab-O-Sil M-5	5	0.5	0.5

The ingredients were mixed in the same manner as in Examples 1—2. The mixture was subjected to compression in a tableting machine having a 0.281 x 0.625 inch (7.14 x 15.88 mm) punch under a compression pressure of 4000 psi (276 bar) to make 10,000 capsule shaped tablets bisected on one side from the treated Methocel K4M and 1000 capsule shaped tablets from the treated and dried Methocel K4M.

The tablets from the treated Methocel K4M had an average weight of 724 mg and a thickness of 0.250—0.260 inches (6.35—6.60 mm) while the tablets from the treated and dried Methocel K4M had an average weight of 714 mg and a thickness of 0.250—0.260 inches (6.35—6.60 mm).

The hardness, friability and release rate of the 650 mg aspirin tablets were determined as described earlier to give the following results:

Example No.	3		4	
Methocel K4M	Treated		Treated-Dried	
Hardness, kg	8.0—10.0		7.0—8.0	
Friability, %	0.2		0.48	
Release rate Hour	%	Cumulative %	%	Cumulative %
1	12.5	12.5	10.7	10.7
2	12.5	25.0	12.1	22.8
3	12.5	37.5	14.4	37.2
4	12.5	50.0	13.2	50.4
5	15.4	65.4	16.7	67.1
6	10.5	75.9	12.8	79.9
7	11.0	86.9	11.6	91.5
8	5.4	92.3	4.9	96.4
9	2.8	95.1	3.1	99.5

EXAMPLE 5

Controlled release 650 mg aspirin tablets containing 2.7% Methocel E4M and 6.3% Methocel K4M were prepared from untreated hydroxypropylmethylcelluloses with moisture contents in the range of 2—3%.

The 650 mg aspirin tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Aspirin	650	650
2	Methocel E4M	19.5	19.5
3	Methocel K4M	45.5	45.5
4	Lubritab	7	7
5	Cab-O-Sil M-5	0.5	0.5

Ingredient 1 was placed in a bag. Ingredients 2 and 3 were added and mixed with ingredient 1. Ingredients 4 and 5 were mixed with the blend of ingredients 1, 2 and 3 for 20 minutes. The mixture was subjected to compression in a tableting machine having a 0.281 x 0.625 inch (7.14 x 15.88 mm) punch under a compression pressure of 5000 psi (345 bar) to make 100 capsule shaped tablets bisected on one side.

The average weight of the tablets was 717 mg and the thickness was 0.250—0.260 inches (6.35—6.60 mm).

The hardness, friability and release rate of the 650 mg aspirin tablets were determined as described earlier to give the following results:

Hardness, kg	7.0—9.0	
Friability, %	0.78	
Release rate Hour	%	Cumulative %
1	23.1	23.1
2	36.1	59.2
3	19.7	78.9
4	15.5	94.4
5	5.2	99.6

EXAMPLE 6

Controlled release 650 mg aspirin tablets containing 2.7% Methocel M50E and 6.3% Methocel K15M were prepared from the untreated Hydroxypropylmethylcelluloses with moisture contents in the range of 2—3%.

The 650 mg aspirin tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Aspirin	650	650
2	Methocel E50	19.5	19.5
3	Methocel K15M	45.5	45.5
4	Lubritab	7	7
5	Cab-O-Sil M-5	0.5	0.5

The ingredients were mixed as described in Example 5. The mixture was tableted under a compression pressure of 5000 psi (345 bar) using a 0.281 x 0.625 inch (7.14 x 15.88 mm) punch to

make 1000 capsul shaped tablets bisected on one side.

The average weight of the tablets was 717 mg and the thickness was 0.250—0.260 inches (6.35 t 6.60 mm).

The hardness, friability and release rate of the 650 mg aspirin tablets were determined as described earlier to give the following results:

Hardness, kg	7.5—9.0	
Friability, %	0.38	
Release rate Hour	%	Cumulative %
1	12.7	12.7
2	12.7	25.4
3	13.3	38.7
4	12.5	51.2
5	15.4	66.6
6	13.4	80.0
7	11.8	91.8
8	6.3	98.1

These results demonstrate that effective release rates are obtained from mixtures of hydroxypropylmethylcelluloses when at least one of the polymers has a molecular weight above 50,000.

Examples 7—12 describe the preparation of controlled release 300 mg theophylline tablets.

EXAMPLE 7

Controlled release 300 mg theophylline tablets containing 19.4% of Methocel K4M were prepared from untreated Methocel K4M having a moisture content of 2.5%.

The 300-mg theophylline tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Theophylline, anhydrous	153	306
2	Methocel K4M	37.5	75
3	Cab-O-Sil M-5	0.75	1.5
4	Stearic acid	1.75	3.5

Ingredients 1 and 2 were mixed, ingredients 3 and 4 were added and the mixture was then blended for 20 minutes. Tablets were prepared under a compression pressure of 5000 psi (345 bar) using a 0.300 x 0.545 inch (7.62 x 13.84 mm) punch to make 500 capsule shaped tablets bisected on one side.

The average weight of the tablets was 392 mg and the thickness was 0.180—0.190 inches (4.57—4.83 mm).

The hardness, friability and release rates of the 300 mg theophylline tablets were determined in the usual manner to give the following results:

Hardness, kg	6.0—8.0
Friability, %	0.2

Release rate Hour	%	Cumulative %
1	19.2	19.2
2	12.7	31.9
3	12.3	44.2
4	11.0	55.2
5	11.0	66.2
6	11.7	77.9
7	10.0	87.9
8	5.6	93.5
9	6.1	99.6

EXAMPLE 8

Controlled release 300 mg theophylline tablets containing 19.4% of Methocel K15M were prepared from untreated Methocel K15M having a moisture content of 2.0%.

The 300 mg theophylline tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Theophylline, anhydrous	153	306
2	Methocel K15M	37.5	75
3	Cab-O-Sil M-5	0.75	1.5
4	Stearic acid	1.75	3.5

The ingredients were mixed as described in Example 7 and tableted under a compression pressure of 5000 psi (345 bar) using a 0.300 x 0.545 inch (7.62 x 13.84 mm) punch to make 500 capsule shaped tablets bisected on one side.

The average weight of the tablets was 388 mg and the thickness was 0.180—0.190 inches (4.57—4.83 mm).

The hardness, friability and release rates of the 300 mg theophylline tablets were determined in the usual manner to give the following results:

Hardness, kg	7.5—8.5	
Friability, %	0.14	
Release rate Hour	%	Cumulative %
1	17.0	17.0
2	12.8	29.8
3	9.7	39.5
4	8.8	48.3
5	8.2	56.5
6	8.0	64.5
7	7.6	72.1
8	7.1	79.2
9	7.7	86.9
10	5.4	92.3
11	2.9	95.2
12	3.7	98.9

EXAMPLE 9

Controlled release 300 mg theophylline tablets containing 17.0% of Methocel K4M and 7.3% of Methocel K15M were prepared from the untreated polymers, each containing 2.0% of moisture.

The 300 mg theophylline tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Theophylline, anhydrous	306	306
2	Methocel K4M	70	70
3	Methocel K15M	30	30
4	Cab-O-Sil M-5	1.5	1.5
5	Stearic acid	3.5	3.5

The ingredients were mixed as described in Example 7, adding the premixed Methocel K4M and Methocel K15M to the theophylline and, after mixing, adding the excipient ingredients 4 and 5. Tablets were prepared under 5000 psi (345 bar) pressure using a 0.300 x 0.545 inch (7.62 x 13.84 mm) punch to make 1000 capsule shaped tablets having an average weight of 406 mg and a thickness of 0.193—0.203 inches (4.90—5.16 mm).

The hardness, friability and release rates were determined as described earlier to give the following results:

Hardness, kg	4.0—8.0	
Friability, %	0.39	
Release rate Hour	%	Cumulative %
1	11.4	11.4
2	6.8	18.2
3	7.5	25.7
4	7.3	33.0
5	8.4	41.4
6	8.9	50.3
7	8.7	59.0
8	11.7	70.7
9	4.4	75.1
10	5.9	81.0
11	6.3	87.3
12	8.4	95.7
13	4.4	100.1

EXAMPLE 10

Controlled release 300 mg theophylline tablets containing 22.4% of Methocel K4M were prepared from Methocel K4M which was exposed to 85% humidity for 24 hours and then dried at 120°F (49°C) to a moisture content of 4.5%.

The 300-mg theophylline tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Theophylline, anhydrous	612	306
2	Methocel K4M	180	90
3	Cab-O-Sil M-5	3	1.5
4	Stearic acid	7	3.5

The ingredients were mixed as described in Example 7. The resultant mixture was tableted under 5000 psi (345 bar) compression pressure using a 0.300 × 0.545 inch (7.62 × 13.84 mm) punch to make 2000 capsule shaped tablets.

The average weight of the tablets was 400 mg and the thickness was 0.185—0.195 inches (4.70—4.95 mm).

The hardness, friability and release rates of the 300 mg theophylline tablets were determined in the usual manner to give the following results:

Hardness, kg	5.0—7.0	
Friability, %	0,3	
Release rate Hour	%	Cumulative %
1	15.7	15.7
2	11.2	26.9
3	9.6	36.5
4	10.9	47.4
5	10.5	57.9
6	10.6	68.5
7	15.5	84.0
8	7.0	91.0

EXAMPLES 11—12

Tablets with 300 mg of theophylline, containing 19.4% of low molecular weight Methocel K35 or Methocel K100, were prepared from untreated Methocel K35 having a number average molecular weight of 19,440 or untreated Methocel K100 having a number average molecular weight of 26,880. The moisture contents of the untreated Hydroxypropylmethylcelluloses were in the range of 2—3%.

The 300 mg theophylline tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Theophylline, anhydrous	153	306
2	Methocel K35 or K100	37.5	75
3	Cab-O-Sil M-5	0.75	1.5
4	Stearic acid	1.75	3.5

The ingredients were mixed as described in Example 7 and tableted under 5000 psi (345 bar) pressure using a 0.300 × 0.545 inch (7.62 × 13.84 mm) punch to make 500 capsule shaped tablets bisected on one side.

The average weight of the Methocel K35 talets was 390 mg while that of the Methocel K100 tablets was 379 mg. The thickness of the former tablets was 0.180—0.190 inches (4.57—4.83 mm) while that of the latter tablets was 0.175—0.185 inches (4.45—4.70 mm).

The hardness, friability and release rates of the 300 mg theophylline tablets were determined as described earlier to give the following results:

Example No.	11		12	
Methocel	K35		K100	
Hardness, kg	6.5—8.0		5.4—7.5	
Friability, %	0.3		0.2	
Release rate Hour	%	Cumulative %	%	Cumulative %
1	85.7	85.7	92.9	92.8
2	15.4	101.1	2.8	95.6

These results demonstrate that hydroxypropylmethylcelluloses having a methoxyl content of 19—24 weight-% are ineffective as the sole component of the carrier base when their number average molecular weight is below 50,000.

Examples 13—15 describe the preparation of controlled release 80 mg isosorbide dinitrate tablets.

EXAMPLE 13

Controlled release 80 mg isosorbide dinitrate tablets containing 13.5% of Methocel K4M and 5.8% of Methocel K15M were prepared from the untreated hydroxypropylmethylcelluloses having moisture contents in the range of 2—3%.

The 80 mg isosorbide dinitrate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Isosorbide dinitrate (25% in lactose)	652.8	326.4
2	Methocel K4M	112	56
3	Methocel K15M	48	24
4	Stearic acid	12	6
5	Silica gel (Syloid 244)	6	3

Ingredients 2 and 3 were premixed and added to ingredient 1. After these ingredients were mixed for 15 minutes, a mixture of ingredients 4 and 5, which had passed through a 20 mesh sieve, was added and the resultant mixture was blended for 20 minutes. The mixture was tableted under a pressure of 5000 psi (345 bar) using a 0.300 x 0.545 inch (7.62 x 13.84 mm) punch to prepare 2000 capsule shaped bisected tablets.

The average weight of the tablets was 422 mg and the thickness was 0.182—0.192 inches (4.62—4.88 mm).

The hardness and friability of the 80 mg isosorbid dinitrate tablets were determined as described earlier. The release rates were determined using solutions having the pH indicated in the following tabl .

Hardness, kg	9.0—11.0		
Friability, %	0.15		
Release rate Hour	pH	%	Cumulative %
1	1.5	15.8	15.8
2	4.5	10.6	26.4
3	6.9	10.5	36.9
4	6.9	8.1	45.0
5	6.9	7.4	52.4
6	6.9	6.6	59.0
7	7.2	8.0	67.0
8	7.2	5.7	72.7
9	7.2	6.7	79.4
10	7.2	12.9	92.3
11	7.2	6.2	98.5

EXAMPLE 14

Controlled release 80 mg isosorbide dinitrate tablets containing 5.8% of Methocel K4M and 13.5% of Methocel K15M were prepared from the untreated hydroxypropylmethylcelluloses having moisture contents in the range of 2—3%.

The 80 mg isosorbide dinitrate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Isosorbide dinitrate (25% in lactose)	652.8	326.4
2	Methocel K4M	48	24
3	Methocel K15M	112	56
4	Stearic acid	12	6
5	Syloid 244	6	3

The ingredients were mixed as described in Example 13. The mixture was tableted under 6000 psi (414 bar) pressure using a 0.300 x 0.545 inch (7.62x 13.84 mm punch to make 2000 capsule shaped tablets.

The average weight of the tablets was 414 mg and the thickness was 0.180—0.190 inches (4.57—4.83 mm).

The hardness, friability and release rates of the 80 mg isosorbide dinitrate tablets were determined as described in Example 13 and gave the following results:

Hardness, kg	9.0—12.0	
Friability, %	0.16	
Release rate Hour	%	Cumulative %
1	11.9	11.9
2	7.6	19.5
3	7.3	26.8
4	7.0	33.8
5	10.4	44.2
6	9.9	54.1
7	7.8	61.9
8	7.1	69.0
9	6.1	75.1
10	4.7	79.8
11	3.9	83.7
12	3.5	87.2
13	10.3	97.5
14	3.0	100.5

EXAMPLE 15

Controlled release 80 mg isosorbide dinitrate tablets containing 9.6% of Methocel K4M and 9.6% of Methocel E4M were prepared from the untreated Methocel K4M containing 2.8% moisture and the untreated Methocel E4M containing 2.5% moisture.

The 80 mg isosorbide dinitrate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Isosorbide dinitrate (25% in lactose)	326.4	326.4
2	Methocel K4M	40	40
3	Methocel E4M	40	40
4	Stearic acid	6	6
5	Syloid 244	3	3

The ingredients were mixed as described in Exampl 13. The mixture was tableted under 6000 psi (414 bar) pressure to make 100 capsule shaped tabl ts, using a 0.300 x 0.545 inch (7.62 x 13.84 mm) punch.

The average weight of the tablets was 418 mg and the thickness was 0.189—0.195 inches (4.80—4.95 mm).

The hardness, friability and release rates of the 80 mg isosorbide dinitrate tablets were determined as described in Example 13 and gave the following results:

Hardness, kg	6.5—8.5	
Friability, %	0.2	
Release rate Hour	%	Cumulative %
1	40.7	40.7
2	11.2	51.9
3	7.2	59.1
4	7.3	66.4
5	6.7	73.1
6	5.7	78.8
7	7.9	86.7
7	3.5	90.2
9	6.0	96.2

Examples 16—19 describe the preparation of controlled release 300 mg lithium carbonate tablets.

EXAMPLE 16

Controlled release 300 mg lithium carbonate tablets containing 24.8% of Methocel K15M were prepared from Methocel K15M which had been exposed to 85% humidity for 24 hours and then dried in a forced air oven at 120°F (49°C) until the moisture content was 5.0%.

The 300 mg lithium carbonate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Lithium carbonate	300	300
2	Methocel K15M	100	100
3	Cherry Flavour	1.2	1.2
4	Magnesium stearate	1.6	1.6

Ingredients 1 and 2 were mixed, ingredient 3 was added and mixed in, followed by the addition of ingredient 4. After mixing for 20 minutes, the mixture was tableted under 5000 psi (345 bar) compression pressure using a 13/32 inch (10.32 mm) tool to prepare 1000 round, flat faced beveled tablets bisected on one side.

The average weight of the tablets was 395 mg and the thickness was 0.120—0.140 inches (3.05—2.56 mm).

The hardness and friability of the 300 mg lithium carbonate tablets were determined as described earlier. The release rates were determined using solutions having the pH indicated in the following table:

	Hardness, kg	6.0—9.0							
	Friability, %	0.29							
	Release rate Hour	pH	%	Cumulative %	Hour	pH	%	Cumulative %	
	1	1.2	14.2	14.2	13	7.5	3.6	72.5	
	2	2.5	11.3	25.5	14	7.5	3.9	76.4	
	3	4.5	5.6	31.1	15	7.5	3.5	79.9	
	4	7.0	5.4	36.5	16	7.5	3.3	83.2	
	5	7.0	5.3	41.8	17	7.5	4.1	87.3	
	6	7.5	3.9	45.7	18	7.5	2.7	90.0	
	7	7.5	4.0	49.7	19	7.5	2.5	92.5	
	8	7.5	3.3	53.0	20	7.5	2.2	94.7	
	9	7.5	4.2	57.2	21	7.5	2.1	96.8	
	10	7.5	4.0	61.2	22	7.5	1.7	98.5	
	11	7.5	3.7	64.9	23	7.5	1.6	100.1	
	12	7.5	4.0	68.9	24	7.5	1.2	101.3	

EXAMPLE 17

Controlled release 300 mg lithium carbonate tablets containing 14.2% of Methocel K15M were prepared using Methocel K15M which had been humidified in an 85% humidity chamber and then dried at 120°F (49°C) to a moisture content of 5.0%.

The 300 mg lithium carbonate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Lithium carbonate	300	300
2	Methocel K15M	50	50
3	Cherry flavour	1.2	1.2
4	Magnesium stearate	1.6	1.6

The ingredients were mixed as described in Example 16 and the mixture was tableted under a pressure of 5000 psi (345 bar) using an 11/32 inch (8.73 mm) tool to prepare 1000 round, flat beveled tablets.

The average weight of the tablets was 354 mg and the thickness was 0.155—0.165 inches (3.94—4.19 mm).

The hardness, friability and release rates of the 300 mg lithium carbonate tablets were determined as described in Example 16 and gave the following results:

Hardness, kg Friability, %		3.8—4.0 0.25	
	Releas rate Hour	%	Cumulative %
	1	23.2	23.3
	2	11.0	34.3
	3	10.5	44.8
	4	8.5	53.3
	5	8.3	61.6
	6	6.8	68.4
	7	7.6	76.0
	8	5.4	81.4
	9	5.3	86.7
	10	4.3	91.0
	11	3.2	94.2
	12	4.7	98.9

EXAMPLE 18

Controlled release 300 mg lithium carbonate tablets containg 19.9% of Methocel K15M were prepared using untreated Methocel K15M having a moixture content of 1.5%.

The 300 mg lithium carbonate tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Lithium carbonate	300	300
2	Methocel K15M	75	75
3	Magnesium stearate	0.8	0.8
4	Cab-O-Sil M-5	1.0	1.0

The ingredients were mixed as described in Example 16. An 11/32 inch (8.73 mm) flat faced bevel tool was used to prepare 1000 white round tablets under 5000 psi (345 bar) pressure. The average weight of the tablets was 380 mg, the thickness was 0.170—0.180 inches (4.32—4.57 mm) and the hardness was 6.0—6.5 kg.

EXAMPLE 19

Controlled release 300 mg lithium carbonate tablets containing 19.9% of Methocel K4M were prepared using untreated Methocel K4M having a moisture content of 2.0%.

The tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Lithium carbonate	300	300
2	Methocel K4M	75	75
3	Magnesium stearate	0.8	0.8
4	Cab-O-Sil M-5	1.0	1.0

The ingredients were mixed as described in Example 16 and the mixture was compressed using an 11/32 inch (8.73 mm) flat faced bevel tool to prepare 1000 white round tablets. The average weight of the 300 mg lithium carbonate tablets was 376 mg, the thickness was 0.165—0.170 inches (4.19—4.32 mm) and the hardness was 6.0 kg.

Examples 20—22 described the preparation of controlled release nitroglycerin tablets.

EXAMPLES 20—21

Controlled release 6.5 mg nitroglycerin tablets containing 24% of Methocel K4M were prepared from untreated Methocel K4M having a moisture content of 2.5% as well as from Methocel K4M which had been humidified and then dried at 120°F (49°C) to a moisture content of 5.0%, as described earlier.

The 6.5 mg nitroglycerin tablets were prepared from the following ingredients:

	Ingredients	Untreated Methocel K4M grams	Treated Methocel K4M grams	mg/tablet
1	Nitroglycerin (10% in lactose)	130	195	65
2	Lactose, anhydrous	80	120	40
3	Methocel K4M	70	105	35
4	FDC Red. No. 3	0.6	0.9	0.3
5	Stearic acid	6	9	3
6	Syloid 244	2	3	1
7	Cab-O-Sil M-5	2	—	1

Ingredients 1, 2, 3 and 4 were mixed together and passed through a 20 mesh sieve. Ingredients 5 and 6, and 7 when used, were mixed, passed through a 20 mesh sieve and then mixed with the mixture of the other ingredients. After 20 minutes of blending, the mixture was compressed using a 9/32 inch (7.14 mm) tool to prepare 2000 pink, round and concave shaped tablets disected on one side from the untreated Methocel K4M and 3000 similar tablets from the treated Methocel K4M.

The tablets from the untreated Methocel K4M had an average weight of 150 mg and a thickness of 0.135—0.145 inches (3.43—3.68 mm). The tablets from the treated methocel K4M had an average weight of 148 mg and a thickness of 0.130—0.140 inches (3.30—2.56 mm).

The hardness and friability of the 6.5 mg nitroglycerin tablets were determined in the usual manner. The release rates were determined using solutions having the same pH as used with the isosorbide dinitrate tablets in Examples 13. The results were as follows:

Example No.	20		21	
Methocel K4M	Untreated		Treated	
Hardness, kg	3.0—4.5		3.0—3.5	
Friability, %	0.3		0.3	
Release rate Hour	%	Cumulative %	%	Cumulative %
1	26.6	26.6	23.7	23.7
2	17.5	44.1	13.8	37.5
3	14.2	58.3	13.3	50.8
4	11.6	69.9	18.2	69.0
5	10.0	79.9	16.7	85.7
6	7.7	87.6	12.4	98.1
7	5.4	93.0		
8	3.8	96.8		

EXAMPLE 22

Controlled release 5.5 mg nitroglycerin buccal tablets containing 11.1% of Methocel K4M were prepared from untreated Methocel K4M having a moisture content of 1.6%.

The 5.5 mg nitroglycerin buccal tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Nitroglycerin (10% in lactose)	275	5.5
2	Lactose, anhydrous	237.5	47.5
3	Methocel K4M	35	7
4	Stearic acid	5	1
5	Syloid 244	5	1
6	Cab-O-Sil M-5	5	1

Ingredient 1 was passed through a 20 mesh sieve. Ingredient 2 was added and mixed, followed by ingredient 3. A mixture of ingredients 4, 5 and 6 was added and mixed. The mixture was compressed using a 1/4 inch (6.35 mm) concave tool to prepare 5000 white, round buccal tablets.

The average weight of the tablets was 120 mg, the thickness was 0.130—0.140 inches (3.30—3.56 mm).

EXAMPLE 23

This example describes the preparation of 5.5 mg controlled release phenylpropanolamine base buccal tablets containing 25.8% of Methocel K4M wherein the latter was subjected to humidification in an 85% relative humidity chamber for 24 hours and then dried at 120°F (49°C) to reduce th moisture content to 4.5%.

The 5.5 mg phenylpropanolamine tablets were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Phenylpropanolamine base	11	5.5
2	Lactose, anhydrous	100	50
3	Methocel K4M	40	20
4	Spearmint flavour	1	0.5
5	Peppermint flavour	1	0.5
6	Stearic acid	2	1

Ingredients 1, 2, 4 and 5 were mixed. Ingredient 3 was then added and mixed for 10 minutes. Ingredient 6 was added and the mixture was blended for 20 minutes. The mixture was tableted under 5000 psi (345 bar) pressure using a 1/4 inch (6.35 mm) concave punch to produce 2000 white round buccal tablets.

The average weight of the tablets was 78 mg and the thickness was 0.105—0.110 inches (2.67—2.79 mm). The hardness, friability and release rates of the buccal tablets were determined as described in Example 22 and gave the following results:

Hardness, kg	4.5—6.0	
Friability, %	0.8	
Release rate	Minutes	Cumulative %
	15	27.6
	30	39.0
	45	50.0
	60	60.2
	90	73.0
	120	83.2

EXAMPLE 24

This example describes the preparation of controlled release 600 mg potassium chloride lozenges containing 24.8% of untreated Methocel K15M.

The 600 mg lozenges were prepared from the following ingredients:

	Ingredients	grams	mg/tablet
1	Potassium chloride	600	600
2	Methocel K15M	200	200
3	Stearic acid	8	8

Ingredient 1 was passed thr ugh a 40 mesh sieve. Ingredient 2 was added and mixed with ingredient 1. Ingredient 3 was passed through a 40 mesh sieve and then mixed with ingredients 1 and 2 for 20 minutes.

The mixture was compressed under 5000 psi (345 bar) using a 7/16 inch (11.11 mm) deep concave punch to prepare 1000 round mottled white lozenges.

The average weight of the lozenges was 810 mg and the thickness was 0.255—0.265 inches (6.48—6.73 mm).

The hardness, friability and release rate of the lozenges were determined as described in Example 22 and gave the following results:

Hardness, kg	6.0—8.5	
Friability, %	0.13	
Release rate	Hour	Cucumulative %
	1	71.2
	2	87.4
	3	99.3

Examples 25 to 27 disclose compositions containing anti-inflammatory drugs such a ibuprofen, flurbiprofen, diclofenac, indomethacin and naproxen.

EXAMPLE 25

Controlled release 700 mg ibuprofen tablets containing 9.5% of Methocel K4M and 9.0% of Methocel K15M were prepared from the untreated hydroxypropylmethylcelluloses having moisture contents in the range of 2.0—3.0%.

A tablet having the following compositions was prepared in the usual manner:

	Ingredients	mg/tablet
1	Ibuprofen	700
2	PVP	20
3	Methocel K4M	85
4	Methocel K15M	80
5	Syloid	5
6	Stearic acid	1

The tablets were compressed using 0.750" x 0.300" (19.05 x 7.62 mm) capsule-shaped bisected punches at a compressional force of about 4000 lbs/sq in. (276 bar) to obtain a tablet of average weight of 893 mg and a hardness of 8 to 10 kg.

EXAMPLE 26

Controlled release 200 mg flurbiprofen tablets containing 12.4% of Methocel K4M and 10.2% of Methocel K15M were prepared from the untreated hydroxypropylmethylcelluloses having moisture contents in the range of 2.0—3.0%.

A tablet having the following composition was prepared in the usual manner:

	Ingredients	mg/tablet
1	Flurbiprofen	200
2	Methocel K4M	33
3	Methocel K15M	27
4	Stearic acid	5
5	Cab-O-Sil M-5	1

Tablets were compressed using 0.281" x 0.625" (7.14 x 15.88 mm) capsule-shaped bisected punches at a compressional pressure of 4000 t 6000 lbs/sq. in. (276 to 414 bar) to obtain a tablet of average weight of 270 mg and a hardness of 6 to 8 kg.

EXAMPLE 27

Controlled release 100 mg diclofenac tablets containing 8.5% of Methocel K4M and 12.8% of Methocel K15M were prepared from the untreated hydroxypropylmethylcelluloses having moisture contents in the rnage of 2.0—3.0%.

A tablet having the following composition was prepared in the usual manner:

	Ingredients	mg/tablet
1	Diclofenac sodium	100
2	P.V.P.	5
3	Methocel K4M	12
4	Methocel K15M	18
5	Stearic acid	5
6	Cab-O-Sil M-5	1

Tablets were compressed using 9/32" (7.14 mm) standard concave round punches at a compressional pressure of 4000 to 6000 lbs/sq. in. (276—414 bar) to give a tablet weight of 144 mg and a hardness of 6 to 8 kg.

The foregoing is exemplary and illustrative of compositions and products corresponding to the present invention, but it is to be understood that they are not limitative since many active medicaments of various types can be employed in the new long-lasting carrier so long as they are absorbable into blood or tissue from the general intestinal tract and other bodily surfaces and areas. The medicaments shown in our co-pending U.K. Patent Application No. 82 35858 may be used in the practice of the present invention and are incorporated herein by reference. The invention is also intended to cover other dosage forms or forms of application of sustained release ingredients such a vaginal and rectal suppositories. The lozenges and tablets particularly act on oral, oropharyngeal, pharyngeal and intestinal regions. The total dosage is governed by usual medical considerations or physicians' directions and when sufficiently large doses of active medicament are incorporated in the unit dosage form, systemic as well as local action is obtained to overcome or control the pathological conditions or disorder being treated.

CLAIMS

1. A carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon administration, the carrier base material being one or more hydroxypropylmethylcelluloses or a mixture of one or more hydroxypropylmethylcelluloses and up to 30% by weight of the mixture of methyl cellulose, sodium carboxymethylcellulose and/or other cellulose ether, and wherein at least one of the hydroxypropylmethylcelluloses has a methoxy content of 16—24 weight-%, a hydroxypropoxyl content of 4—32 weight-% and a number average molecular weight of at least 50,000 and wherein the carrier base material constitutes less than about one third of the weight of the solid unit dosage form.

2. A composition according to claim 1, in which the carrier base material consists of a mixture of one or more hydroxypropylmethylcelluloses and 0—30% of sodium carboxymethylcellulose.

3. A composition according to claim 1, in which the carrier base material consists of a mixture of one or more hydroxypropylmethylcelluloses and 0—30% of methylcellulose or other cellulose ether.

4. A composition according to any of claims 1 to 3, in which the active medicament is a moisture-sensitive material.

5. A composition according to claim 4, in which the moisture-sensitive medicament is selected from aspirin, theophylline, phenacetin, procainamide, nikethamide, polymixin, barbiturates, idoxuridine, hydantoins, angi tensinamide, nitroglycerin, isosorbide dinitrate, benzocaine, scopolamine, meperidine, codeine, morphine, streptomycin, ascorbic acid, sulphonamide drugs, tolbutamide, chlorpheniramine, brompheniramine, phenylephrine, diphenhydramine, penicillins, tropine alkaloids, diethylcarbamazine, dihydroergotamine, caffeine, d xamethasone, and pharmaceutically acceptable salts of any of the above, alkaloid salts and adrenocortical steroid esters.

6. A compositions according to any of claims 1 t 3, in which the active medicament is lithium

carbonate.

7. A composition according to any of claims 1 to 3, in which the active medicament is phenylpropanolamine.

8. A compositions according to any of claims 1 to 3, in which the active medicament is potassium chlorid .

9. A composition according to any of claims 1 to 3, in which the active medicament is an anti-inflammatory drug.

10. A composition according to claim 9, in which the anti-inflammatory drug is selected from ibuprofen, flurbiprofen, diclofenac, indomethacin and naproxen.

11. A composition according to claim 1, substantially as hereinbefore described with reference to any of the Examples.

12. A method for the preparation of a therapeutically active solid unit dosage form having a regular and prolonged release pattern upon administration, which comprises compressing and shaping a mixture of a therapeutically active medicament and a carrier base material consisting of one or more hydroxypropylmethylcelluloses or a mixtures of one of more hydroxypropylmethylcelluloses and up to 30% by weight of the mixture of methylcellulose, sodium carboxymethylcellulose or other cellulose ether, and wherein at least one of the hydroxypropylmethylcelluloses has a methoxyl content of 16—24 weight-%, a hydroxypropoxyl content of 4—32 weight-% and a number average molecular weight of at least 50,000, and wherein the carrier base material constitutes less than about one third of the weight of the solid unit dosage form.

13. A method according to claim 12, substantially as hereinbefore described with reference to any of the Examples.

14. A composition prepared by a method according to claim 12 or 13.

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